Scientific Abstract

Absence of purine nucleoside phosphorylase (PNP) in humans results in severe T-cell immunodeficiency, an autosomal recessive inherited disease which is usually fatal in the first decade of life due to the inability to fight off common infections. Because the symptoms of PNP deficiency are restricted to the hematopoietic system, it may be possible to restore immune function in patients by PNP gene transfer and expression in blood cells. In previous studies, we demonstrated that retroviral-mediated PNP gene transfer corrected the enzyme deficiency as well as the metabolic defect (deoxyguanosine sensitivity) in PNP-deficient murine lymphoma cells, and also corrected proliferative responses in T-cells cultured from a child with the disease. In addition, other investigators have reported encouraging results from trials of gene transfer into lymphocytes as a way of treating severe combined immunodeficiency associated with the absence of adenosine deaminase activity, a condition similar to PNP deficiency. Based on these previous results, a phase I / II study of retroviral-mediated PNP gene transfer targeting lymphocytes will be conducted on two PNP-deficient patients. T- lymphocytes will be harvested from the patient and cultured in artificial capillary cartridges in the presence of anti-CD3 and IL2. The cells will then be transduced twice in the cartridge during the process of expansion and harvested several days thereafter for reinfusion into the patient. Cell harvest, transduction, and infusion will be repeated every two months for the first year. Increasing doses of cells will be infused (10^7 to 10^9 per kg) to assess the safety of the T-cell infusions. In followup studies, PNP gene transfer and expression levels will be assessed monthly to determine the gene transfer frequency and expression level. The goal of the transduction procedure will be to effect >5% transduction in PBL and >5% of the normal level of enzyme expressed in PBL. Finally, the patients will undergo testing for any improvement in immunological function which may be associated with increased PNP activity in PBL. Positive results from this trial will be interpreted as supportive not only for gene therapy trials which seek to treat immunodeficiencies by gene transfer into blood cells, but also for other diseases associated with more systemic symptomatology which may nonetheless respond to treatment by gene transfer and expression in blood cells.